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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/877,220	06/08/2001	Karin Westlund High	265.0019 0101	8535

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MUETING, RAASCH & GEBHARDT, P.A.
P.O. BOX 581415
MINNEAPOLIS, MN 55458

EXAMINER	
BRANNOCK, MICHAEL T	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 12/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/877,220	HIGH ET AL.	
	Examiner	Art Unit	
	Michael Brannock	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *17 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *20,21,24 and 29-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) *34,35,46,47,54 and 55* is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) *30 and 31* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 April 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application: Claims and Amendments

Applicant is notified that the amendments put forth on 8/17/04, have been entered in full.

Response to Amendment

Applicant is notified that any outstanding objection or rejection that is not expressly maintained in this Office action has been withdrawn in view of Applicant's amendments and persuasive arguments.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 20, 21, 32, 33, 36, 37, 42-45 are rejected under 35 U.S.C. 102(b) as being anticipated by Rao et al., Neuron, 19(801-812)1997.

Rao et al., disclose an assay that monitors NR1 subcellular distribution, comprising contacting a neuron with an amount of a compound effective to alter the subcellular distribution of NR1, e.g. APV or Tetrodotoxin (TTX), and activating an NMDA receptor (e.g. by culturing the cells under conditions which allow spontaneous activation of the receptor (as when testing APV) or by adding NMDA (as when testing TTX), see col 1, page 804), and detecting the distribution of NR1 in a neuron, e.g. see Figure 3 and the amount of NR1 in a neuron (see col 1

of page 803 and col 2 of page 805). The claims have been amended to specifically require activation of NMDA receptors on the test and the control cell. This assay was specifically disclosed in Figure 1 at page 802 and discussed in the text beginning in the last paragraph of page 803. In these experiments, the NMDA receptor activation is effected by culturing the cells such that they are allowed to spontaneously activate. Referring to Figure 1, in panels 1A and 1B the NMDA receptor control cells are activated and in panels 1E and 1F the NMDA receptor test cells are activated. In panels 1C and 1D the test cells were not activated. By comparing the subcellular distribution of the NR1 subunits of the control cells with that of the test cells, it was determined that the compound (APV) altered the subcellular distribution of the NR1 subunits and that this alteration was dependent on the activity of the NMDA receptors on the cells.

Applicant's arguments regarding activating the NMDA receptors on control cells have been substantially addressed above and not found persuasive. Applicant asserts that there were no measured changes in the amount of NR1. Regarding claims 20 and 21, the claims claim a method for identifying a compound that alters NR1 subunit distribution, the method of Rao et al., would certainly accomplish this regardless of whether or not the compound used actually produced the effect. This concept holds true for claim 21 as well, because Rao et al. clearly indicate that any change in amount would be measured, see col 1 of page 803; thus the general method, as claimed, is taught by Rao et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 24, 29, 38, 39, 48, 49, 52, 53, 56, 57, 60-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rao et al,., Neuron, 19(801-812)1997 in view of Wang, YT et al., PNAS 93(1721-1725)1996 .

Rao et al., disclose an assay that monitors NR1 subcellular distribution, comprising contacting a neuron with an amount of a compound effective to alter the subcellular distribution of NR1, e.g. APV or Tetrodotoxin (TTX), and activating an NMDA receptor (e.g. by culturing the cells under conditions which allow spontaneous activation of the receptor (as when testing APV) or by adding NMDA (as when testing TTX), see col 1, page 804), and detecting the distribution of NR1 in a neuron, e.g. see Figure 3 and the amount of NR1 in a neuron (see col 1 of page 803 and col 2 of page 805). The central finding of Rao et al. is that it is the activity of the NMDA receptor that regulates its subcellular distribution (see the Title); Rao et al. speculate that phosphorylation may be involved in this regulation but do not specifically mention tyrosine phosphorylation. Wang, YT et al. teach that tyrosine phosphorylation regulates NMDA receptor activity, and use tyrosine kinase inhibitors and tyrosine phosphatase inhibitors to modulate the activity of NMDA receptors (see the Abstract).

Therefore, one of ordinary skill in the art, at the time the invention was made, and with reasonable expectation of success, would be motivated to assay tyrosine kinase inhibitors and tyrosine phosphatase inhibitors as taught by Wang in the method of Rao, the motivation to do so is provided by Rao who teach that activity regulates the subcellular distribution of NMDA receptors and by Wang who teach that tyrosine phosphorylation modulates activity.

Applicant argues that Rao does not teach or suggest that phosphorylation alone will cause redistribution of NMDA receptors. This argument has been fully considered but not deemed persuasive. As admitted by Applicant, Rao speculates that phosphorylation may be a potential molecular mechanism through which redistribution of NMDA receptors resulting from chronic blockade of NMDA receptors with APV occurs. This statement is certainly a suggestion.

Regarding Applicant's arguments for factual support, Applicant argues that Rao do not teach activating the NMDA receptors on the control cell in the absence of an additional compound. This argument has been fully considered but not deemed persuasive. This is exactly what was done as depicted in panels 1A, B and 1E, F.

Applicant argues that Wang teaches a method wherein the NMDA blockage specifically removed, therefore teaching away form the method of Rao and rendering inoperable the combination of Wang and Rao. First, the examiner admits that he may not understand the premise of Applicant's argument. However, one of ordinary skill in the art understands Rao teaches that the level of NMDA receptor activity has an effect on subcellular distribution of the NR1 subunit and that they speculate that phosphorylation could be involved. Wang, YT et al. teach that tyrosine phosphorylation modulates receptor activity. Specifically they teach that tyrosine kinase inhibitors decrease activity and tyrosine phosphatase inhibitors increase the

activity of NMDA receptors (see the Abstract). Thus they teach modulation of activity in both directions (increases and decreases) so it is unclear why Applicant would assert that the two methods would not be amenable to each other.

Claims 38-41, 48-51, 58, 59, 64, 66 and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rao et al,., Neuron, 19(801-812)1997 in view of Ehlers, MD et al., Science 269(1734-1737)1995.

Rao et al., disclose an assay that monitors NR1 subcellular distribution, comprising contacting a neuron with an amount of a compound effective to alter the subcellular distribution of NR1, e.g. APV or Tetrodotoxin (TTX), and activating an NMDA receptor (e.g. by culturing the cells under conditions which allow spontaneous activation of the receptor (as when testing APV) or by adding NMDA (as when testing TTX), see col 1, page 804), and detecting the distribution of NR1 in a neuron, e.g. see Figure 3 and the amount of NR1 in a neuron (see col 1 of page 803 and col 2 of page 805). The central finding of Rao et al. is that it is the activity of the NMDA receptor that regulates its subcellular distribution (see the Title); Rao et al. speculate that phosphorylation may be involved in this regulation but do not specifically mention phosphorylation of the NR1. Ehlers teach that serine phosphorylation of NR1 regulates subcellular distribution of the NMDA receptor, see the Abstract and col 1 of page 1736.

Therefore, one of ordinary skill in the art, at the time the invention was made, and with reasonable expectation of success, would be motivated to assay serine/threonine phosphatase inhibitors and to measure NR1 phosphorylation as taught by Ehlers when practicing the method of Rao, the motivation to do so is provided by Rao who teach that activity regulates the

subcellular distribution of NMDA receptors and by Ehlers who teach that such alterations in subcellular distribution are accompanied by changes in NR1 phosphorylation.

It is noted that Ehlers did not appear to find nuclear translocation of the NR1 subunit, which would appear to be in contradiction to the instant application, however, this may be explained by the absence of NMDA receptor signal transduction mechanisms present in the cell type used by Ehlers and/or by the lack of NMDA receptor activity. It is also noted that the instant specification indicates that changes in NR1 phosphorylation accompany changes in receptor tyrosine kinase activity, however there is no teaching that NR1 is phosphorlyated on tyrosine (see page 29), and it is assumed that the anti-phospho-NR1 antibody referred to on page 29 recognizes a phosphorlyated serine or threonine.

Applicant's arguments regarding Rao have been substantially addressed above, yet not found persuasive.

Applicant argues that the method of Ehlers lacks several important features, e.g. endogenous NMDA receptors, and that combining teachings of Rao and Ehlers would cause both methods to fail. This argument has been fully considered but not deemed persuasive. The experimental methods of Ehler, as pointed to by Applicant, are not being relied on as a basis for the rejection; instead the results of those experiments would motivate one of ordinary skill in the art to modify the methods of Rao to arrive at the instantly claimed invention. Specifically Ehlers teach that serine phosphorylation of NR1 regulates subcellular distribution of the NMDA receptor, see the Abstract and col 1 of page 1736, which would obviously be of importance to anyone practicing the methods of Rao because this provides an explanation for their own findings as directly stated by them.

Allowable Subject Matter

Claims 34, 35, 46, 47, 54, 55 are allowed.

Claims are 30, 31 objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX months.

Please note the new central fax number for official correspondence below:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (571) 272-

0869. The examiner can normally be reached on Mondays through Fridays from 10:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, Ph.D., can be reached at (571) 272-0961. Official papers filed by fax should be directed to 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

MB

ELIZABETH KEMMERER
PRIMARY EXAMINER

December 20, 2004